EUROPEAN PATENT APPLICATION NO. 02797229.8
NOVEL CHIMERIC TNF LIGANDS

DECLARATION OF DR. CHARLES PRUSSAK

I, Dr. Charles Prussak, declare as follows:

1. I am an inventor of the invention that is claimed in this patent application, and a co-author of the Abstract entitled "Membrane-Stabilized Chimeric Tumor Necrosis Factor for Gene Therapy of B Cell Malignancies" ("Abstract").

2. I have reviewed the outstanding Office Action in this application. I understand that a question has arisen regarding whether Domain III of a TNF family molecule is present in the CD154-TNF chimeric molecule that is referred to in the Abstract. In particular, I understand that the Action contends that Domain III is entirely absent from the chimeric molecule, based on a portion of the Abstract which reads as follows: "We generated chimeric TNF genes encoding the receptor-binding domain of TNF spliced onto transmembrane domains of other members of the TNF family." The Examiner has construed the quoted passage as meaning that Domain IV of TNF alpha subdomain was spliced directly onto Domain II of CD154. This is not a correct reading of the Abstract.

3. I respectfully suggest that the Examiner has read the Abstract more literally than may be justified. It should be appreciated that the Abstract was a poster paper intended only to convey that chimeric molecules possessed properties (with respect to minimized release of soluble TNF) not possessed by the non-chimeric molecules discussed. Therefore, the Abstract described the molecules broadly with reference to functional and structural regions, rather than providing a detailed, domain-by-domain description of each molecule.

4. In particular, Domain III of CD154 *was* present and intact in the CD154-TNF chimera described in the Abstract. The passage relied upon by the Examiner for the contrary conclusion does not refer to Domain III at all, but only explains that two functional regions of the CD154 and TNF molecules (the transmembrane and binding regions, respectively) were present in the CD154-TNF chimera as a result of splicing portions of each molecule together.

5. The only portion of the Abstract which specifically referred in any way to the presence or absence of Domain III pertained to a different, non-chimeric molecule, ΔTNF. In the ΔTNF molecule, "we introduced an in-frame deletion to generate a truncated TNF gene (ΔTNF) lacking the known site(s) for cleavage by matrix metalloproteinases." The "site(s)" referred to by this passage are contained in Domain III of CD154, which was therefore retained in these molecules, albeit in modified form.

6. The Office Action also contends that the claims must recite that a transmembrane domain is present in the molecules "since it is undesirable that soluble TNF alpha is generated, a transmembrane domain is essential in the chimeric TNF alpha of the invention." This is not an accurate characterization of how the TNF family molecules function in vivo.

7. The domains of the TNF molecule that play a role in whether it is cleaved from the cell surface are Domains III and IV, which contain cleavage sites. The invention is therefore primarily addressed to these domains. Theoretically, Domains III and IV could be anchored to a cell membrane surface by means other than a transmembrane domain. Such a domain is therefore not an essential part of the claimed molecules of the invention.

I hereby verify that the foregoing is true and correct to the best of my knowledge and information.

Executed at San Diego, California.

DATED: May 8th, 2006

Dr. Charles Prussak